PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	05.08.2005
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
2003.793 WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/051069	09.06.2004	12.06.2003

Applicant
ORGANON IRELAND LTD. et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/051069

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-9 as originally filed

   Claims, Numbers

   1-12 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-9

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-3 and 7-9 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. 20-27,36 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-6 (with respect to industrial applicability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	7-12
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III.

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1. Article 34(4)(a)(i) PCT

Claims 1-6 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

III.2. Article 6 PCT

III.2.1. The terms (i) 'patient with overweight', (ii) 'patient that was having weight gain due to another antipsychotic agent' and (iii) 'patient that needs to be protected against weight increase due to the presence of risk factors for a disease for which overweight is also a risk factor or due to the presence of other weight increasing factors' in claims 1-3 and 7-9 are considered unclear within the meaning of Article 6 PCT to such an extent as to render a meaningful search of the claims impossible.

The description provides explanatory support for term (iii) only for patients suffering from diabetes, cardiovascular diseases or sudden abstinence from smoking (page 2, lines 33-35).

III.2.2. Consequently, an International Search has been carried out for those parts of the claims that appear to be clear, i.e. those parts wherein the group of patients is limited to obese patients, patients having a BMI >= 25 (cf claims 4, 5, 10 and 11) and patients suffering from diabetes, cardiovascular diseases or sudden abstinence from smoking (page 2, lines 33-35).

III.2.3. As the ISR for the present application has been limited to subject-matter as defined under item III.2.2, this Written Opinion has been established only for those parts of the subject-matter of the present claims for which an International Search has been performed, namely those parts that have been specified under item III.2.2 above.

Re Item V.

Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability

V.1. The following documents are referred to:

D1: US 2002/156067 A1 (SVENSSON TORGNY ET AL) 24 October 2002 (2002-10-24)

D2: WO 95 23600 A (AKZO NOBEL NV ;DELBRESSINE LEONARDUS PETRUS C (NL); WIERINGA JOHAN) 8 September 1995 (1995-09-08)

D3: SUSSMAN N: 'Review of atypical antipsychotics and weight gain.' THE JOURNAL OF CLINICAL PSYCHIATRY. UNITED STATES 2001, vol. 62 Suppl 23, 2001, pages 5-12, XP008026085 ISSN: 0160-6689

D4: RUSSELL J M ET AL: 'Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications.' CNS DRUGS. NEW ZEALAND 2001, vol. 15, no. 7, 2001, pages 537-551, XP008026091 ISSN: 1172-7047

D5: ALLISON D B ET AL: 'ANTIPSYCHOTIC-INDUCED WEIGHT GAIN: A COMPREHENSIVE RESEARCH SYNTHESIS' AMERICAN JOURNAL OF PSYCHIATRY, AMERICAN PSYCHIATRIC ASSOCIATION, WASHINGTON, DC, US, vol. 156, no. 11, November 1999 (1999-11), pages 1686-1696, XP001009543 ISSN: 0002-953X

D6: BAZIRE S: 'Schizophrenia' CHEMIST&DRUGGIST, [Online] 3 August 2002 (2002-08-03), pages 17-20, XP002266562 Retrieved from the Internet: <URL:http://www.dotpharmacy.co.uk/up1243.pdf> [retrieved on 2004-01-12]

V.2. Novelty (Article 33(2) PCT)

The present application does meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-12, if limited to the subject-matter as defined under item III.2.2, is new in the sense of Article 33(2) PCT.

V.2.1. Prior art

Document D1 (US2002/156067 A1)

discloses the combined use of a norepinephrine reuptake inhibitor and a neuroleptic agent, including ORG-5222 (= asenapine) for the treatment of diseases of the central nervous system, including schizophrenia and obesity.

Document D2 (WO 95 23600A)

discloses a sublingual or buccal pharmaceutical composition of asenapine for the treatment of mental disorders, including psychosis and schizophrenia (abstract).

V.2.2. The subject-matter of the present claims involves the use of the antipsychotic agent asenapine (= ORG-5222) for the treatment of schizophrenia in overweight or obese patients or in patients which show a predisposition for overweight or obesity. The alleged advantage of asenapine, when compared to other atypical antipsychotic agents, in particular to risperidone, is its reduced tendency to cause significant weight increases in the patients.

V.2.3. Document D1 does not disclose or suggest an activity of asenapine when used as the only active compound as claimed in the present application. Furthermore, schizophrenia appears in a long list of indications mentioned in document D1.

V.2.4. Document D2 discloses the applicability of asenapine in the treatment of schizophrenia, but is silent about a particular selection of patients for which asenapine shows advantageous properties, when compared with other atypical antipsychotics.

The subject-matter of claims 1-12, if limited to the subject-matter as defined under item III.2.2, is therefore considered novel in the sense of Article 33(2) PCT.

V.3. Inventive step (Article 33(3) PCT)

The present application does meet the requirements of Article 33(1) PCT, because the subject-matter of claims 1-12, if limited to the subject-matter as defined under item III.2.2, does involve an inventive step in the sense of Article 33(3) PCT.

V.3.1. Problem to be solved

The problem to be solved by the present invention is the provision of a medicament for the treatment of schizophrenia in patients a) suffering from overweight or obesity, b) having had weight gain due to treatment with another antipsychotic agent or c) having, due to the presence of other weight-increasing factors, a pre-disposition for overweight or obesity.

V.3.2. Solution

The solution as provided by the present invention is to use the atypical antipsychotic asenapine (=ORG-5222).

V.3.3. Prior art

Document D2

discloses asenapine and sublingual or buccal pharmaceutical composition comprising asenapine for the treatment of schizophrenia.

Document D3 (XP008026085)

discloses data on the weight-increasing effects of various antipsychotic agents, including clozapine, olanzapine, sertindole, risperidone and haloperidol after 10 weeks of treatment (Figure 1). The changes in body weight differ significantly from each other, with the atypical antipsychotics clozapine and olanzapine causing the highest gains in body weight and risperidone causing less than 50% of the weight increase of clozapine.

Document D4 (XP008026091)

discloses that "studies have reported that clozapine treatment is associated with an average bodyweight gain of up to 16.2 kg (...) Olanzapine and risperidone are also associated with varying degrees of bodyweight gain, and there are some data to indicate that quetiapine and zotepine also cause this adverse effect. (...) Limited data indicate that ziprasidone and amisulpride are less likely to cause bodyweight gain, but further studies are needed to confirm this" (page 538, paragraph bridging left and right columns).

Document D5 (XP001009543)

discloses that antipsychotic medication using clozapine, olanzapine, thioridazine/mezoridazine, sertindole, chlorpromazine, risperidone, polypharmacy, nonpharmacologic control, haloperidol and fluphenazine resulted in an weight gain after 10 weeks on standard drug doses (figure 1), and that only treatment with ziprasidone and molindone resulted in a lack of weight gain or a reduction of weight, respectively.

Document D6 (XP002266562)

discloses that weight gain is a 'marked' side effect in the treatment with clozapine and olanzapine, a 'moderate' side effect in the treatment with phenothiazines and 'some' side effect in the treatment with butyrophenones, thioxanthenes, benzamides, quetiapine and risperidone (page 19). It is further disclosed that 'Weight gain is a major problem, both in terms of physical problems (hypertension, increased risk of type 2 diabetes, stroke and hypercholesterolaemia) as well as psychological (self-

image) not to mention financial (...) and the adverse effect on compliance. The mechanism is unclear but is unlikely to be increased appetite alone" (page 20, column 2).

V.3.4. Difference between the application and the closest prior art

The difference between the present application and document D2, which has been selected as the closest prior art, is the special section of a group of schizophrenia patients, namely overweight or obese patients, patients for which a treatment with other antipsychotics had resulted in a weight gain and patients with a pre-disposition for overweight or obesity.

V.3.5. Analysis of the presence of an inventive step

The person skilled in the art, knowing about the activity of asenapine as an atypical antipsychotic (from D2), and aware of any or all of documents D3-D6 would, in view of the significantly varying tendencies of antipsychotic agents to cause weight gain, not directly conclude from that knowledge that asenapine has a beneficial (i.e. not/little increasing) effect on the weight of a schizophrenia patient during the treatment.

The experimental data presented in the present application show the results of a comparative test using asenapine and risperidone. In a test group of similar size, asenapine caused a weight gain of $\geq 7\%$ only for two subjects whereas in the risperidone group a weight gain of $\geq 7\%$ was detected in 8 subjects.

Therefore, the experimental data demonstrate a superior effect of asenapine on the body weight of schizophrenia patients when compared with risperidone, which is not even one of the antipsychotics showing a high weight gain.

Consequently, the presence of an inventive step in the sense of Article 33(3) PCT can be recognised for the subject-matter of claims 1-12, if limited to the subject-matter as defined under item III.2.2.

V.4. Industrial applicability (Article 33(4) PCT)

For the assessment of the present claims 1-6 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.